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10/748,033	12/30/2003	Peter Muhlradt	29473/11899A	7597

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EXAMINER	
AUDET, MAURY A	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,033	MUHLRADT ET AL.	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-12* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response of 6/18/07 and 2/20/07 is acknowledged. Claims 1, 4, and 6-12 are examined on the merits. Claim 5 is withdrawn as being drawn to non-elected subject matter.

Election/Restrictions

As noted before, Applicant's election of Group I, claims 1-12, as drawn to a lipopeptide/lipoprotein structure wherein loci Y is SEQ ID NOS: 3, 7, 8, or 10 (peptide species election being MALP-2 (e.g. stereochemically opposing SEQ ID NO: 8 or 10), wherein the species of the remainder of the lipopeptide/lipoprotein structure sidechain groups include: R1 is C15 alkyl; R2 is C15 alkyl; X is S; Z1 is H; Z2 is H; and W is Co (n is therefore not applicable)) in the reply filed on 06/21/2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-12 are examined on the merits as drawn to the elected invention (lipopeptide/lipoprotein structure wherein Y is only SEQ ID NOS: 3, 7, 8, or 10).

Response to Arguments

On page 7 of the 2/20/07 response, Applicant states that:

> Applicants note that the experimental results reported herein are based on an incorrect interpretation of the stereo configuration of the tested compounds (i.e., the results ascribed to the "R" configuration apply to the "S" configuration and vice versa). Specifically, Example 2 of the present application references a synthetic procedure according to Metzger *et al.* (1991). Metzger *et al.* incorrectly indicated that compounds having the "R" configuration are synthesized using (S)-(-)-glycidol as

> starting material. Instead, compounds having the "R" configuration are synthesized using (R)-~(+)-glycidol as starting material. Thus, in view of Metzger, the applicants mistakenly attributed the results for the "R" configuration to the "S" configuration and vice versa. Nonetheless, applicants had possession of the claimed subject matter at the time of the application filing.

Based on the above, it is doubt as to "what is right and what is wrong" and what has written description and what does not. Thus, some form of evidence must be provided to corroborate the above statements, of which, this Examiner is not sure of the form/channel to guide Applicant (Applicant may wish to first consult the MPEP for any guidance). Until such time as the written description for the presently claimed invention is certain, a New Matter rejection is necessitated and the grounds for rejection are maintained based on the reasons of record.

Claim Rejections - 35 USC § 112 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, and 6-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Namely, the stereo configuration of the present compounds, upon which arguments directed for the patentability thereof have been based in responding the outstanding rejections/prior art of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 4, and 6-12, as drawn to the elected species described at the outset, are rejected under 35 U.S.C. 103(a) as being unpatentable over Muhlradt et al. (J. Exp. Med., June 2, 1997, pp. 1951-1958) in view of WO 98/27110 (GESELLSHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF))) and Fidler et al. (US 4916118), is maintained for the reasons of record, until such time as the subject matter for which the invention has written description is properly determined.

Muhlradt et al. teach the synthetic "S-[2,3-bispalmitoyloxy-(2S)-propyl]cysteinyl-GNNDESNISFKEK" compound (p. 1955 Fig. 2B; Applicant's elected species structure SEQ ID NOS: 3 and 10); based on the native form isolated from a mycoplasma clone, specifically a Mycoplasma fermentans clone, which is water-soluble (abstract, introduction); having "highest specific MSA [macrophage stimulating activity] of so far described" (page 1952, sec. 2); which may be useable in such solutions as potent macrophage and B cell activators and vaccines, like other MSA compounds (page 1955, 2nd column, 1st para.). Muhlradt et al. also teach that a "wealth of information about which particular moieties of the lipopeptides are functionally important has been forthcoming from synthesis and assay of various analogues. Thus, the presence of both ester-bound fatty acids is a prerequisite for biological activity, whereas the amide-bound fatty acid was found to be dispensable" (p. 1955, last para.)". Muhlradt et al.

places no import as to the lipopeptide/lipoprotein structure * asymmetric carbon atom has the absolute configuration R when X = S (sulfur) [as opposed to (native??? assumed) absolute configuration S when X = S (sulfur) – see 35 USC section 112 2nd below also)) OR that either configuration bears any physiological impact on the compounds ability to function in stimulating immune system response to infection.

WO 98/27110 teach the native "S-(2,3-dihydroxypropyl)cysteine-GNNDESNISFKEK" compound isolated from a mycoplasma clone, specifically a Mycoplasma fermentans clone, which is water-soluble (abstract, page 3); as well as for an agent [i.e. for treatment] containing the afore-mentioned peptide [Applicant's elected species structure, e.g. SEQ ID NOS: 3 and 10].

Fidler et al. teach the use of "2-palmitoyl derivatives . . . lipopetides having immunomodulating properties" (column 7, lines 33-35, 39-4) in pharmaceuticals as macrophage stimulators (column 8, lines 37-41).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the lipopeptide/lipoprotein structure with the * asymmetric carbon atom in EITHER the absolute configuration NATIVE S or R when X = S (sulfur) in Muhlradt et al., because the reference advantageously teaches that a " wealth of information about *which particular moieties of the lipopeptides are functionally important* has been forthcoming from synthesis and assay of various analogues. Thus, the presence of both ester-bound fatty acids is a prerequisite for biological activity, whereas the amide-bound fatty acid was found to be dispensable" (p. 1955, last para.)"; with no mention (nor in Applicant's present specification) that altering the * asymmetric carbon atom from it's *native* absolute configuration S when X = S (sulfur), to R configuration; impacts any unexpected results in terms of the compounds ability to

stimulate infection treating chemical pathways, based on routine reconfiguration of *native* absolute configuration S to R configuration when X = S (sulfur), absent evidence to the contrary.

It also would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use pharmaceutical agents for infection treatment (e.g. wound treatment) incorporating 2-palmitoylthio derivatives and lipopeptides with the (elected MALP-2) structure S-[2,3-bispalmitoyloxy-(2R)-propyl]cysteinyl-GNNDESNISFKEK, in Muhlradt et al., because WO 98/27110 advantageously teach agents using native MALP-2 compounds for stimulating infection-treating pathways and because Fidler et al. advantageously teach that lipopeptides with 2-palmitoylthio derivatives, like that of Muhlradt and WO 98/27100, in a pharmaceutical composition exhibit macrophage stimulating activity which beneficially produces an immune system response in the recipient [i.e. against infection].

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 1, 4, and 6-12 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6-8, and 10-11 of copending Application No. 10/509,917 in view of Muhlradt et al. (J. Exp. Med., June 2, 1997, pp. 1951-1958), is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '917 are drawn to any use of the same lipopeptide/lipoprotein wherein Y may be virtually any peptide, such as e.g. SEQ ID NO: 3.

The '917 patent was not expressly claimed for infection/wound treatment, but rather any use. Since the use is not expressly claimed, the use must be read in light of the specification of '917, which contemplates use of compounds such as SEQ ID NO: 3 for IgA stimulation which in turn stimulated protection of mucosal membranes from infection (e.g. which would include infections within wounds therein)(page 10, 2nd para.) Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to treat wounds using SEQ ID NO: 3 in the present invention, based on the advantageous teachings of '917 for use such compounds as SEQ ID NO: 3 for anti-infection stimulation of IgA.

Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the lipopeptide/lipoprotein structure with the * asymmetric carbon atom in EITHER the absolute configuration NATIVE S or R when X = S (sulfur) in '917 in view of Muhlradt et al. (discussed above under 35 USC 103), because Muhlradt et al. advantageously teaches that a " wealth of information about *which particular moieties of the lipopeptides are functionally important* has been forthcoming from synthesis and assay of various analogues. Thus, the presence of both ester-bound fatty acids is a prerequisite for biological activity, whereas the amide-bound fatty acid was found to be dispensable" (p. 1955, last para.)"; with no mention (nor in Applicant's present specification) that altering the * asymmetric carbon atom from it's *native* absolute configuration S when X = S (sulfur), to R configuration; impacts any unexpected results in terms of the compounds ability to stimulate infection treating chemical pathways, based on routine reconfiguration of *native* absolute configuration S to R configuration when X = S (sulfur), absent evidence to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1, 4, and 6-12, as drawn to SEQ ID NOS: 3, 7, 8 or 10, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is

maintained for the reasons of record, until such time as the subject matter for which the invention has written description is properly determined. Claim 1 requires that the lipopeptide/lipoprotein structure * asymmetric carbon atom to have the absolute configuration R when X = S (sulfur) (as opposed to abandoned parent application 09/716,778, which required * asymmetric carbon atom to have the (native??? assumed) absolute configuration S when X = S (sulfur)). According the sequence identifier information, only SEQ ID NO: 10 is clearly in the absolute configuration R when X is S. Whereas, SEQ ID NO: 10 is indefinite, since it appears to be in the absolute configuration S when X is S, contrary to the limitations set by claim 1. Additionally, SEQ ID NO: 7 is also indefinite, since it contemplates absolute configurations of both R and S when X is S. Finally, SEQ ID NO: 3 appears definite, like SEQ ID NO: 10 (which SEQ ID NO: 10 includes in it's entirety as part of the greater structure, as do SEQ ID NOS: 7 and 8) is simply the peptide itself, without the other required attributes/components of the structure, and is open ended in terms of attributes, allowing for absolute configuration R when X is S. Clarification or amendment is required, and if the above is correct based on the amendment of absolute configuration S to R, it is simply suggested that SEQ ID NOS: 7 and 8 be deleted from the claim language. While, other claim amendments are made to indicate e.g. wherein Y of the lipoprotein/lipopeptide structure of claim 1 is SEQ ID NO: 3 and wherein the lipopeptide/lipoprotein of claim 1 IS SEQ ID NO: 10.

Observation

The two primary references cited as prior art of record in the present application are both Applicant's works. Should Applicant respond with amendments deleting various sidechain

group options for the lipopeptide/lipoprotein structure of claim 1, in an attempt to overcome the prior art of record, it is strongly suggested that Applicant clearly argue/describe 1) every structural limitation described in those references, and 2) why the remaining sidechain alternations (not in the reference(s)), for use the same/similar method of using nearly identical compounds provides some unobvious effect in this method or unexpected result; rising to the level of unobvious substitution.

Conclusion

Applicant's amendment/arguments necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 571-272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 8/20/2007

CHRISTOPHER R. TATE
PRIMARY EXAMINER